REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the commentary that follows. Claims 1-38 are pending in the application. Claims 13-36 are withdrawn without prejudice from consideration. Applicants reserve the right to file a divisional patent application in relation to any aspect of this non-elected subject matter. Claims 37 and 38 are supported in the specification on page 4, lines 5-7 and page 4, lines 13-15. New claims 39 and 40 are supported in the specification at page 5, line 16 through page 6 line 23 and page 16, lines 6-12, respectively. Claims 1, 3, 4, 6-9, 11, 12, and 37-40 are now pending.

Rejection of claims under 35 USC §112, First Paragraph

The Examiner has rejected claims 1-7 under 35 USC § 112, first paragraph, on the ground that while being enabling for methods of diagnosing lung damage by measuring an increase in pulmonary surfactant A and/or pulmonary surfactant B, it does not enable the diagnosis of lung damage based on measuring for decreases in SP-A or SP-B or measuring either increases or decreases in SP-C or SP-D.

Without prejudice and to advance prosecution, applicants amend these claims to specify that an increase in pulmonary surfactant levels, in the context of detecting lung damage, is the modulation that the application describes.

The Examiner has further rejected claims 1-7 on the ground that the specification teaches that SP-A and SP-B levels are increased in lung damage but there is no teaching provided in support of a correlation between monitoring lung damage and changes in SP-C or SP-D levels. Similarly, the Examiner has rejected claims 8-12 as well for failing to teach a correlation between monitoring lung damage and SP-C or SP-D.

Applicants disagree with the Examiner's rationale for rejection because the applicants discovery found that changes in the alveolar capillary membrane permeability, lead to the leakage of surfactant molecules. The surfactant molecules released include pulmonary surfactant molecules. Even though this discovery was

exemplified with reference to SP-A and SP-B, it also supports the release of SP-C and SP-D from changes in alveolar capillary membrane permeability.

Rejections of claims under 35 USC §112 - Second Paragraph

The Examiner has alleged that claims 1-12 are indefinite because the defined analysis requires a modulation or comparison and does not define what the screened amount is compared to.

Applicants disagree with the Examiner's rejection because "modulation" is clearly defined in the specification, at page 10, lines 14-22, in the context of a comparative analysis between a test result and a normal reference level. As noted above, in any event, applicants have amended the claims, without prejudice, to embody the notion of a comparison between a test result and a normal reference level. The term "normal reference level" is defined and discussed in the specification at page 10, lines 14-22.

Rejection of claims under 35 USC §102

The Examiner has rejected the claims on the ground that they lack novelty in light of Honda *et al.* (1996), Abe *et al.* (1995), and Doyle *et al.* (1997), respectively. Applicants would emphasize, however, that these publications do not anticipate the presently claimed invention because every recited element is not set out in any give reference, as noted below.

Honda et al (1996)

Applicant argues that Honda (1996) merely notes that surfactant proteins SP-A and SP-D are elevated in serum from patients with a "disease", specifying being idiopathic interstitial pneumonia. Applicants would draw the Examiner's attention to the fact that the present application, by contrast, is directed to the detection of surfactant proteins in body fluids as a means for monitoring or detecting the existence of changes in the extent of *lung damage* and *not* a disease condition, per se.

Specifically, "disease" implies a clinical manifestation whereas "damage" does not. In this regard, a "disease" may be caused by any one or more forms of physical or physiological damage and this damage may not necessarily be known or identified.

Accordingly, these forms of damage may not necessarily form the basis of a screening protocol for a "disease." Many forms of physical damage also are not necessarily associated with a disease condition (e.g., damaged ligaments or muscles). Accordingly, screening for a disease condition is a distinct matter to screening for a specific form of physical damage, which damage may or may not be associated with a disease condition. Further, the publication in question neither discloses nor suggests whether SP-A and SP-D are associated with any form of specific physical damage.

In this regard, the Examiner's attention is drawn to the fact that lung damage may be implicit in some forms of disease but that the corollary is not always true. For example, asymptomatic smokers (refer example 4 of the subject patent application) exhibit alveolo-capillary membrane damage but not lung disease. Accordingly, the method of the present application is directed to screening for a particular form of physical damage, irrespective of whether it is associated with a disease condition. Further, the present invention provides a means of detecting and monitoring this form of damage, which means were not available or known prior to the advent of this invention. The present invention also provides a degree of sensitivity that was not available in the field previously and is not contemplated in the cited prior art. Accordingly, it is respectfully submitted that the cited prior art documents do not anticipate or even presage the presently claimed invention.

Abe et al. (1995)

Applicants respectfully disagree with the Examiner's rejection of the present claims as anticipated by the Abe et al. (1995) reference. Applicant again requests that the Examiner note that the presently claimed invention is not directed to diagnosing disease conditions, per se, but is directed to the diagnosis of lung damage based on changes to serum pulmonary surfactant levels. Additionally, the present invention claims the detection of very early stage lung damage (being lung damage which is otherwise undetectable without the aid of one or more invasive procedures). Most importantly, the present invention provides a means of identifying the existence of lung damage in an asymptomatic patient and, further, facilitates the prediction of an individual's predisposition to developing severe lung damage (see claims 3, 39, and

40). This invention is based on the discovery that serum surfactant levels are inextricably linked to the existence, or not, of lung damage.

The disclosures in the Japanese language article by Abe *et al.* are summarized in an English abstract. Briefly, the Abe *et al.* reference assesses the utility of measuring SP-A in patients with various lung diseases relative to healthy volunteers. As explained above the subject matter of the present invention relates to lung damage rather than lung disease.

Even if a disease condition, such as pulmonary alveolar proteinosis, were known to be associated with lung damage, moreover, this damage would only represent one of a large number of physical or physiological forms of damage that might be associated with that disease condition. Accordingly, it would not be possible, on the basis of such limited disclosure of data, to draw a correlation between the elevation of SP-A and any specific aspect of the disease condition.

Additionally, only approximately 70% of patients with this disease condition exhibited elevated systemic SP-A levels. Absent any detailed study of the differences, in the nature of the disease condition, between those patients who did exhibit elevated SP-A levels to those who did not, one of ordinary skill could not possibly have correlated changes in these levels with the existence or absence of lung damage. On the basis of these data alone, the elevation of SP-A levels could have been due to any one or more of the causes or symptoms of this condition, which were present in some of these patients (approximately 70%) but not all.

If we accept, arguendo, that this disease condition is one known to exhibit lung damage, then these results actually would teach away from the notion that elevated SP-A levels are associated with lung damage. Were such an association expected, in other words, some percentage closer to 100% of patients should have exhibited elevated SP-A levels. Since prior art implicates no basis for detecting SP-A in some forms of this disease but not in others, there likewise is nothing to have suggested the relationship between SP-A and the phenomenon of lung damage, as such. In particular, these results would imply that there are features of the disease condition that in some instances but not in others facilitate the secretion of SP-A. Thus, the

reference does not correlate increased SP-A levels with the onset of lung damage as claimed in the present invention (see claims 3, 39, and 40).

In relation to the existence of lung damage, per se, the mere association between changes in SP-A levels and the existence of a lung disease by itself does not indicate that the changes in SP-A level are in any way associated with the onset of lung damage. Even the authors themselves state only that their results would teach using SP-A levels to diagnose the three specifically recited disease conditions and do not comment any further in relation to any other disease condition in respect of which this test would be useful or to the mechanism by which SP-A levels become systemically elevated.

Further, the fact that analyses were made in relation to patients with idiopathic interstitial pneumonia, pulmonary alveolar proteinosis, and collagen disease with interstitial pneumonia certainly would not have suggested, let alone anticipated, the notion that one could use SP-A as a means of detecting early stage lung damage (*i.e.*, damage that has occurred in asymptomatic patients) or a predisposition to the development of severe lung damage (see claim 3, 39 and 40).

Accordingly, on the basis of the teachings provided by Abe *et al.* there is neither teaching nor suggestion of identifying lung damage, as presently claimed. It is respectfully submitted that the claimed invention is novel in light of these brief and inconclusive results, which were generated in relation to three forms of disease of the lung and not lung damage, per se (either in the symptomatic or asymptomatic context). Applicants therefore respectfully request withdrawal of the Examiner's rejection.

Doyle et al (1997)

The abstract of Doyle *et al.* provides preliminary data in relation to the level of surfactant proteins A and B in the serum of normal individuals as compared to those individuals with no evidence of cardiorespiratory disease, those with cardiogenic pulmonary oedema, those with acute respiratory distress syndrome, and those at risk. The results indicate that serum SP-A and B were elevated in patients with acute cardiogenic pulmonary oedema and acute respiratory distress syndrome, respectively.

By contrast, the results in relation to patients at risk or with no evidence of cardiorespiratory disease were not significantly higher than normal patients.

The data provided in the *Doyle et al.* abstract neither disclose nor suggest the detection of early stage lung damage. (We note that the patients analyzed for this abstract were all ventilated patients and therefore no longer suffering from early stage damage.) The abstract clearly is limited to providing a basic comparison of SP-A and SP-B levels in normal patients versus patients who have already developed severe lung damage. Further, this abstract in fact teaches away from the notion of screening for surfactant levels as a means of diagnosing a predisposition to developing severe lung damage since the patients categorized as being at risk in fact showed no significant change in SP-A or SP-B levels as compared to normal patients.

With regard to the issue of screening for SP-A, SP-B and/or ratios thereof as an indicator of lung damage, this should be considered in the context of the prior art as it existed as at 1994. In light of the review article by Pittet *et al.* (1997) (Appendix B), it is clear that there was much research being directed towards the identification of biological markers of lung damage. However, although various groups were identifying markers, such as inflammatory mediators, which were modulated in patients suffering from lung damage, none of these markers had been found to function as an exclusive indicator of the onset of lung damage. Rather, changes in the levels of these markers (such as TNF, IL-1, IL-8, IL-10 and other inflammatory mediators) also could have been indicative of many other unrelated conditions. Accordingly, there was an ongoing interest in identifying markers which specifically indicated the onset of lung damage and which exhibited a high level of sensitivity. The article by Pittet *et al.* provides an eloquent review of the various categories of markers which were known as of 1997. Upon reviewing this article, it is clear that the authors do not regard any of the markers analyzed up to 1997 as providing either a specific or highly sensitive indication as to lung damage. In this regard, the authors at page 1191 discuss the results by Doyle *et al.* and neither disclose nor suggest that SP-A and SP-B serum levels provide a specific marker of lung damage.

The 1997 Doyle abstract provides no suggestion that pulmonary surfactant levels are any more sensitive than any other marker, such as an inflammatory mediator.

Thus, there is no disclosure of its applicability in this regard nor teaching to suggest that pulmonary surfactant would be any more likely than any other marker to provide a specific and sensitive indicator in this regard. Accordingly, the statement in the last sentence of the Doyle *et al.* abstract, that "SP-B enters more readily and may ultimately provide a better indicator of lung trauma" should be considered in light of the surrounding prior art, and subsequently published prior art, which effectively qualify this statement. In this regard, the results detailed in the Doyle *et al.* abstract to some extent mirror those of Abe *et al* which were examining surfactant levels in lung trauma patients at around the same time, and also found that surfactant levels were elevated. As with the Doyle *et al.* abstract, this Japanese group did not foreshadow that surfactant levels could be used to predict and monitor lung damage nor that it provided a highly specific and sensitive marker of the onset of lung damage.

Accordingly, it is arguable that this abstract neither discloses nor teaches toward the role of serum surfactant levels as a specific and highly sensitive indicator of lung damage. Further, there is neither disclosure nor teaching towards the notion that changes in surfactant level could be used to diagnose early stage lung damage, being lung damage in individuals who are otherwise not exhibiting outward symptoms of lung damage.

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested. The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date 29 May 2003

By S. A. Bent

FOLEY & LARDNER
3000 K Street, N.W., Suite 500
Washington, D.C. 20007-5143
Telephone: (202) 672-5404
Facsimile: (202) 672-5399

Stephen A. Bent
Attorney for Applicant
Registration No. 29,768

Should additional fees be necessary in connection with the filing of this paper, or if a petition for extension of time is required for timely acceptance of same, the Commissioner is hereby authorized to charge Deposit Account No. 19-0741 for any such fees; and applicant(s) hereby petition for any needed extension of time.